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| EXAMINER | |
|---|---|
| GANGLE, BRIAN J | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/564,264 | WINTER ET AL. | |
| | Examiner | Art Unit | |
| | Brian J. Gangle | 1645 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *25 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-71* is/are pending in the application.

4a) Of the above claim(s) *23-71* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 January 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/9/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

Applicant's election with traverse of Group I, and the strain BLR(DE3) in the reply filed on 7/25/2007 is acknowledged. The traversal is on the following ground(s):

1. That a search and examination of all claims may be made without imposing a serious burden on the examiner.

2. That the instant case was filed under 35 USC 371, thus the PCT rules regarding lack of unity must be followed. Since the International Searching Authority did not set forth a lack of unity in the parent PCT case, there is no lack of unity.

3. That the examiner is incorrect in stating that the groups lack the same or corresponding technical features since the examiner stated that the technical feature linking the groups is a mature SpeB polypeptide.

This is not found persuasive for the following reasons:

Regarding argument 1, search and examination burden is not a criteria when determining the propriety of a restriction requirement under the PCT rules regarding lack of unity.

Regarding argument 2, each application is examined on its own merits, and the actions of the International Searching Authority have no binding impact upon the instant case. Furthermore, the fact the International Searching Authority chose not to set forth a finding of lack of unity does not mean that unity exists; it merely means that the International Searching Authority chose not to set forth a finding of lack of unity. In the instant case, the PCT rules regarding lack of unity were properly followed, as set forth in the restriction requirement.

Regarding argument 3, the examiner never stated that "the groups lack the same or corresponding technical features." The examiner stated that the groups lack the same or corresponding *special* technical features. According to PCT Rule 13.2, a technical feature must define a contribution over the art in order to be a *special* technical feature. As set forth previously, the feature linking the groups in this case does not define a contribution over the art; therefore, there is no *special* technical feature linking the groups, and the restriction is therefore proper.

The requirement is still deemed proper and is therefore made FINAL.

Upon further consideration, the restriction between the strains of *E. coli* in claims 11 and 22, is withdrawn. The strains are closely related functional equivalents and the choice of one strain versus another is considered obvious.

Claims 1-71 are currently pending. Claims 23-71 are withdrawn as being drawn to non-elected inventions. Claims 1-22 are currently under examination.

### *Information Disclosure Statement*

The information disclosure statement, filed 1/9/2006, has been considered. An initialed copy is enclosed.

### *Specification*

The use of the trademarks ROSETTA, TUNER, and ORIGAMI have been noted in this application on page 30. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

It is noted that the cited occurrences of improper use are only exemplary and applicant should review the specification to correct any other use of trademarks.

### *Claim Objections*

Claims 5 and 16 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The parent claim requires production of mature SpeB, which is necessarily immunogenic in mammals. Therefore, claims 5 and 16 are not further limiting.

### *Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-8 and 12-19 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The term "host cell" is not specifically defined by the specification as being non-human or isolated. The scope of the claim, therefore, encompasses a human being, which is non-statutory subject matter. As such, the recitation of the limitation "non-human" or "isolated" would be remedial. See 1077 O.G. 24, April 21, 1987.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6 and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a vast genus of methods for expressing a mature SpeB polypeptide, wherein the mature SpeB polypeptide binds and is neutralized by antibodies that are cross-reactive with wild-type SpeB polypeptide. To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that Applicant has possession the claimed invention. To adequately describe the genus of methods for expressing a mature SpeB

polypeptide, wherein the mature SpeB polypeptide binds and is neutralized by antibodies that are cross-reactive with wild-type SpeB polypeptide, applicant must adequately describe the antigenic determinants (immunoepitopes) that elicit the required cross-reactive and neutralizing antibodies directed against SpeB polypeptides.

The specification, however, does not disclose distinguishing and identifying features of a representative number of members of the genus of immunogenic polypeptides to which the claims are drawn, such as a correlation between the structure of the immunoepitope and its recited function (to elicit the required cross-reactive and neutralizing antibodies directed against SpeB polypeptides), so that the skilled artisan could immediately envision, or recognize at least a substantial number of members of the claimed genus of immunogenic compositions. Moreover, the specification fails to disclose which amino acid residues are essential to the function of the immunoepitope or which amino acids might be replaced so that the resultant immunoepitope retains the activity of its parent, or by which other amino acids the essential amino acids might be replaced so that the resultant immunoepitope retains the activity of its parent. Therefore, since the specification fails to adequately describe at least a substantial number of members of the genus of immunoepitopes to which the claims are based; the specification fails to adequately describe at least a substantial number of members of the claimed genus of methods for expressing a mature SpeB polypeptide, wherein the mature SpeB polypeptide binds and is neutralized by antibodies that are cross-reactive with wild-type SpeB polypeptide.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a

mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

*The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description'' Requirement* (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104).

The *Guidelines* further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. As evidenced by Greenspan *et al.* (Nature Biotechnol. 7: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan *et al.* recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan *et al.*, an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes that can elicit a protective immune response to a given pathogen can only be identified empirically. Therefore, absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of immunoepitopes, the skilled artisan could not immediately recognize or distinguish members of the claimed genus of methods for expressing a mature SpeB polypeptide, wherein the mature SpeB polypeptide binds and is neutralized by antibodies that are cross-reactive with wild-type SpeB polypeptide. Therefore, because the art is unpredictable, in accordance with the *Guidelines*, the description of immunoepitopes (antigenic determinants) is not deemed representative of the genus to which the claims refer. Hence, the

claims do not meet the written description requirements.

Claims 8 and 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the plasmid represented by the designation pCRT7-CTTOPO is required in order to practice the invention. Specifically, it is noted that claims 8 and 19 recite deposited material. The deposit of biological organisms is considered by the Examiner to be necessary for the enablement of the current invention (see 37 CRF 1.808(a)).

If the deposit is made under terms of the Budapest Treaty, then an affidavit or declaration by Applicants or person(s) associated with the patent owner (assignee) who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty *and* that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit, or declaration by Applicants or person(s) associated with the patent owner (assignee) who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the following criteria have been met:

1) during the pendency of the application, access to the deposit will be afforded to one determined by the Commissioner to be entitled thereto;

2) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent; and

3) the deposits will be maintained for a term of at least thirty (30) years from the date of the deposit or for the enforceable life of the patent or for a period of at least five (5) years after the most recent request for the furnishing of a sample of the deposited material, whichever is longest; and

4) a viability statement in accordance with the provisions of 37 CFR 1.807; and

5) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition, the identifying information set forth in 37 CRF 1.809(d) should be added to the specification. See 37 CFR 1.803 - 1.809 for additional explanation of these requirements.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 6, 8, 11, 15, 17, 19, and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4 and 15 are rendered vague and indefinite by the phrase "wherein the cysteine at amino acid residue 192 of the mature SpeB polypeptide is substituted by a serine." The specification does not provide a specific sequence for the SpeB polypeptide, and there are multiple sequences for this protein known in the art. While these sequences agree on the location of the cysteine at residue 192, the sequences are disclosed in Genbank and are therefore changeable. As such, the metes and bounds of the limitation are rendered uncertain.

Claims 6 and 19 are rendered vague and indefinite by the phrase "wherein an antibody specific for the mature SpeB polypeptide cross-reacts with a wild-type SpeB polypeptide and neutralizes SpeB polypeptide activity." It is not clear whether this phrase refers to additional method steps or whether this phrase is merely describing a property of the mature SpeB polypeptide.

Claims 11 and 22 contain the trademarks/trade names ROSETTA, TUNER, and ORIGAMI. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the

trademarks/trade names are used to identify/describe specific *E. coli* strains and, accordingly, the identification/description is indefinite.

Claims 8 and 19 are rendered vague and indefinite by the use of the terms, "pET, pRSET, pCRT7-CTTOPO, and pIVeX." These terms constitute laboratory designations that do not provide any structural or functional limitation. Therefore, it is not clear what the metes and bounds of the instantly claimed invention are.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 12-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gubba *et al.* (Infect. Immun., 66:765-770, 1998, ID filed 1/9/2006) in view of Matsuka *et al.* (Infect. Immun., 67:4326-4333, 1999).

The instant claims are drawn to a method for recombinantly expressing a mature *Streptococcus pyogenes* exotoxin B (SpeB) polypeptide in a host cell, the method comprising transforming, transducing, transfecting or infecting a host cell with a plasmid comprising a polynucleotide sequence encoding a SpeB pro-polypeptide domain and a plasmid comprising a polynucleotide sequence encoding a mature SpeB polypeptide, and culturing the host cell under conditions which permit the expression of the mature SpeB polypeptide and the SpeB pro-polypeptide domain by the host cell, and wherein the mature SpeB polypeptide is soluble in the host cell (claim 12); wherein the SpeB pro-polypeptide domain is further defined as a polypeptide comprising amino acid residues 28 through 145 of SEQ ID NO:2 (claim 13); wherein the mature SpeB polypeptide is further defined as a polypeptide comprising amino acid residues 146 through 398 of SEQ ID NO:2 (claim 14); wherein the cysteine at amino acid residue 192 of the mature SpeB polypeptide is substituted by a serine (claim 15); wherein the mature SpeB polypeptide is immunogenic in a mammalian host (claim 16); wherein an antibody

specific for the mature SpeB polypeptide cross-reacts with a wild-type SpeB polypeptide and neutralizes SpeB polypeptide activity (claim 17); wherein the plasmid is a T7 promoter-containing plasmid (claim 18); wherein the plasmid is selected from the group consisting of pET, pRSET, pCRT7-CTTOPO and pIVeX (claim 19); wherein the host cell is a bacterial cell (claim 20), specifically, *E. coli* (claim 21); wherein the E. coli is a strain selected from the group consisting of BLR(DE3), BLR(DE3)pLysS, AD494(DE3), AD494(DE3)pLysS, BL21(DE3), BL21(DE3) pLysS, BL21(DE3)pLysE, BL21(DE3)pLacI, BL21trxB(DE3), BL21trxB(DE3)pLysS, HMS174(DE3), HMS174(DE3)pLysS, HMS174(DE3)pLysE, Origami(DE3), Origami(DE3)pLysS, Origami(DE3)pLysE, Origami(DE3)pLacI, OrigamiB(DE3), OrigamiB(DE3)pLysS, OrigamiB(DE3)pLysE, OrigamiB(DE3)pLacI, Rosetta(DE3), Rosetta(DE3)pLysS, Rosetta(DE3)pLysE, Rosetta(DE3)pLacI, Tuner(DE3), Tuner(DE3)pLysS and Tuner(DE3)pLacI (claim 22).

Gubba *et al.* disclose a method of recombinantly expressing a mature SpeB polypeptide in *E. coli* wherein the host cells are transformed with separate plasmids containing the pro-polypeptide of SpeB (with the sequence of residues 28-145 of SEQ ID NO:2, except that residue 111 is alanine rather than valine) and the mature SpeB polypeptide (with the sequence of residues 146-398 of SEQ ID NO:2, except that the cysteine of residue 192 is substituted with serine, also referred to as C192S SpeB) (see Figure 1). Said C192S SpeB polypeptide was immunogenic in humans and reacted with the wild-type SpeB (page 767, column 1, paragraphs 4-5 and page 768, column 2, paragraph 4).

Gubba *et al.* differs from the instant invention in that the pro-polypeptide and the mature polypeptide are either expressed as a single zymogen or are expressed from different plasmids in different cells rather than on two plasmids within the same cell. Additionally, amino acid 111 is alanine rather than valine and residue 192 is cysteine rather than serine. Gubba *et al.* further do not use a T7 promoter or one of the specific plasmids or host cells listed in claims 8 and 11.

Matsuka *et al.* disclose a method of recombinantly expressing a mature SpeB polypeptide using a pET expression vector in BL21(DE3) host cells (an expression system which makes use of a T7 promoter, as evidenced by the Novagen catalog, 2001, pages 2-3) (see page 4327, paragraph bridging columns 1-2). Matsuka disclose that the mature SpeB polypeptide is insoluble when expressed by itself; the pro-polypeptide portion of SpeB is necessary for proper

folding and solubility, which is consistent with data from other authors suggesting that the pro-segments of cysteine proteases play an important role in the folding of the protein (page 4331, column 2, paragraph 2).

Therefore, it would have been obvious, at the time of invention, to use the plasmids of Gubba *et al.* to express both the SpeB pro-polypeptide and the mature SpeB polypeptide in the same cell, so that the mature SpeB polypeptide would be properly folded and soluble. It would also have been obvious to use the pET expression vector in BL21(DE3) *E. coli* cells because this expression vector is standard in the art for its ease of use.

One would have had a reasonable expectation of success because the vectors disclosed by Matsuka *et al.* are standard expression vectors and because expressing multiple plasmids in the same cell has been performed for many years.

With regard to claims 2 and 3, while Gubba *et al.* disclose a SpeB pro-polypeptide and a mature SpeB pro-polypeptide, amino acid 111 is alanine rather than valine and residue 192 is cysteine rather than serine. However, each element of the claimed invention was known in the prior art. In this case, there are multiple alleles of SpeB known in the art (as evidenced by Kapur *et al.*, PNAS, 90:7676-7680, 1993). The wild type contains serine at residue 192 and Kapur *et al.*, among others, disclose an allele with alanine at residue 111. These elements could have been combined by one of ordinary skill in the art and each element would have performed the same function as it did separately with predictable results. Thus, it would have been obvious to one of ordinary skill in the art to use any of the various wild type SpeB alleles because, according to the Supreme Court in *KSR International Co. v. Teleflex Inc.*, No. 04-1350 (U.S. Apr. 30, 2007), it is obvious to combine prior art elements according to known methods to yield predictable results.

Claims 1-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gubba *et al.* (Infect. Immun., 66:765-770, 1998, ID filed 1/9/2006) and Matsuka *et al.* (Infect. Immun., 67:4326-4333, 1999) as applied to claims 12-22 above, and further in view of Tan (Prot. Expression and Purification, 21:224-234, 2001).

Gubba *et al.* and Matsuka *et al.*, as combined over claims 12-22, is set forth above. The combination as set forth above does not teach the method where a single, polycistronic plasmid encodes both the SpeB pro-polypeptide and the mature SpeB polypeptide (claims 1-11 are

analogous to claims 12-22, except that the polypeptides are on a polycistronic plasmid rather than on two plasmids).

Tan discloses a modular polycistronic expression system for overexpressing protein complexes in *E. coli* (see abstract). BL21(DE3)pLysS *E. coli* cells were used to express pST36 plasmids (which are T7 expression plasmids) (see page 225, column 1, paragraph 3). The polycistronic expression vector disclosed is useful because the ability to coexpress several polypeptides from one plasmid removes the need for multiple expression plasmids which would require different origins of replication and selection markers for coexpression (page 226, column 2, paragraph 1).

Therefore, it would have been obvious, at the time of invention, to express the SpeB pro-polypeptide and the mature SpeB polypeptide using a polycistronic expression vector in order to take advantage of the ability to coexpress several polypeptides from one plasmid and to avoid the need for multiple expression plasmids which would require different origins of replication and selection markers for coexpression.

One would have had a reasonable expectation of success because Tan showed that polycistronic plasmids are capable of coexpressing multiple genes.

### *Conclusion*

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian J. Gangle whose telephone number is (571) 272-1181. The examiner can normally be reached on M-F 7-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brian Gangle
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